Remarks

Applicants request consideration on the merits of the above-referenced patent application.

I. Amendments to claims

Claims 1-9 and 11-15 are pending. This Amendment C amends claims 1, 2, and 13. The pending claims, including the amendments, are shown in the previous section. Applicants submit that the amendments do not introduce new matter, and are permissible under MPEP §2163.07. Specifically:

Claims 1, 2, and 13 have been amended to replace the phrase "labeled substrate" with the phrase "substrate having a label" and the phrase "the amount of substrate remaining or differentially-charged product formed" with the phrase "how much substrate is remaining or how much differentially-charged product is formed".

Claim 2 has been amended to replace the phrase "thereby effecting the conversion of" with the phrase "thereby effecting the converting".

Applicants reserve the right to pursue any canceled and/or unclaimed subject matter in one or more later-filed divisional and/or continuation applications.

II. Response to rejection of claims 1-9 & 11-15 under 35 U.S.C. §112, first paragraph

The Office action rejects claims 1-9 and 11-15 under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement because the phrase "wherein the steps of coupling and detecting are performed sequentially without removing the substrate or product that is not coupled to the resin" is not found in the originally-filed specification. Applicants request withdrawal of the rejection. As acknowledged by the office action, the specification describes a single-step assay. Namely, Applicants describe an assay in which the addition of ion-exchange resin to the enzyme reaction results in substantially separating the unreacted labeled substrate from the newly-formed differentially-charged product in a single step. *See* Applicants' specification at, for example, page 3, lines 4-21. Applicants also describe measuring the amount of the unreacted labeled substrate or the formed differentially-charged product without removing the unreacted labeled substrate or formed differentially-charged product that is not bound to the ion-exchange resin. *See* Applicants' specification at, for example, page 5, lines

22-28; and pages 14-15 (Examples 1 and 2). Thus, the June 28, 2004 amendment to independent claims 1, 2, and 13 complies with 35 U.S.C. §112, first paragraph.

III. Response to rejection of claims 1-9 & 11-15 under 35 U.S.C. §112, second paragraph

The Office action rejects claims 1-9 and 11-15 under 35 U.S.C. §112, second paragraph for being indefinite because the phrases "the label", "the amount of substrate", and "thereby effecting the conversion" lack antecedent basis. Applicants request withdrawal of the rejection. Applicants submit that the amendments to independent claims 1, 2, and 13 obviate the rejection.

IV. Response to the rejection of claims 1-3, 5, 6, 8, 9, 11, & 13 under 35 U.S.C. §102(b)

The Office action rejects claims 1-3, 5, 6, 8, 9, 11, and 13 under 35 U.S.C. §102(b) for lacking novelty in view of Cerretani et al. Applicants request withdrawal of the rejection.

A. Claim 1

As discussed in the June 28, 2004 response to the April 27, 2004 Office action, Cerretani et al. remove the negatively-charged unreacted substrate and N-terminal cleavage product bound to the ion-exchange resin from the positively-charged C-terminal cleavage product that is in solution by centrifugation before detecting and quantifying the positively-charged C-terminal cleavage product. Claim 1, on the other hand, is directed to a method of determining enzyme activity in which the material bound to the ion-exchange resin (*i.e.*, the unreacted substrate or formed product depending on the particular assay) is not removed before the detection of the unreacted substrate or formed product. Thus, claim 1 is novel over Cerretani et al.

B. Claim 2

Like claim 1, claim 2 is directed to a method of determining enzyme activity in which the material bound to the ion-exchange resin is not removed before the detection of the unreacted substrate or formed product. Thus, claim 2 is novel over Cerretani et al. for at least the same reasons discussed above with respect to claim 1.

C. **Claims 3, 5, 6, 8, 9 & 11**

Claims 3, 5, 6, 8, 9, and 11 depend from claims 1 or 2 (or from claims depending from those claims), and are therefore novel over Cerretani et al. for at least the same reasons discussed above with respect to claims 1 and 2.

D. **Claim 13**

Claim 13 is directed to a method of identifying a molecule, compound, or composition that affects enzyme activity in which, like in claim 1, the material bound to the ion-exchange resin is not removed before the detection of the unreacted substrate or formed product. Thus, claim 13 is novel over Cerretani et al. for at least the same reasons discussed above with respect to claim 1.

V. **Response to the rejection of claims 4, 7, 12, 14 & under 35 U.S.C. §103(a)**

The Office action rejects claims 4, 7, 12, and 14-15 under 35 U.S.C. §103(a) for being obvious over Cerretani et al. in view of Sandmann et al. or Strulovici (U.S. Patent No. 5,759,787). Applicants request withdrawal of this rejection.

The present invention is directed to a method of determining enzyme activity in which the assayed enzyme converts a labeled substrate into a differentially-charged product. The addition of an ion-exchange resin results in (1) the coupling of either the substrate or product to the resin; and (2) substantial separation of the substrate from product in a single step. The detection and quantification of either the product or substrate is performed without removing the material that is not coupled to the resin (*i.e.*, the unreacted substrate or formed product depending on the particular assay).

As discussed above, Cerretani et al. remove the negatively-charged unreacted substrate and N-terminal cleavage product bound to the ion-exchange resin from the positively-charged C-terminal cleavage product that is in solution by centrifugation before they detect and quantify the positively-charged C-terminal cleavage product. Thus, the present invention is non-obvious over Cerretani et al.

Sandmann et al. describe how to measure the activity of mevalonate kinase, mevalonate phosphate kinase, and mevalonate pyrophosphate anhydrodecarboxylase by utilizing radioactive

substrates (*i.e.*, mevalonic acid ("MVA"), mevalonic acid phosphate ("MVAP"), and mevalonic acid pyrophosphate ("MVAPP")). Sandmann et al. separate the substrate (*i.e.*, MVA) and all products (*i.e.*, MVA, MVAP, MVAPP, and isopentyl pyrophosphate ("IPP")) by anion exchange chromatography (*i.e.*, Sandmann et al. do not describe the formation of a differentially-charged product and substantial separation of the substrate from product(s) in a single step). And Sandmann et al. detect and quantify the substrate and products after sequentially eluting them from the chromatography column (in fact, Sandmann et al. explain that the separation of MVAPP and IPP requires further enzyme treatment of the eluted sample and subsequent separation). Thus, the present invention is non-obvious over Sandmann et al.

Strulovici describes how to measure the activity of various kinases by exposing biotinylated substrates bound to streptavidin-coated plates to a kinase, treating the plates with antibodies that recognize only the modified (*i.e.*, phosphorylated) substrate, and detecting the modified substrate by colorimetry or chemiluminescence. Strulovici does not describe the formation of a differentially-charged product and substantial separation of the substrate from product by utilizing an ion-exchange resin. Thus, the present invention is non-obvious over Strulovici.

The present invention is also non-obvious over the combined teachings of Cerretani et al., Sandmann et al., and Strulovici because those references fail to teach, suggest, or provide motivation for combining their teachings. As noted in MPEP §2143.01:

> the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.

Here, the references do not provide any express motivation to combine their teachings. And there is no implied motivation to combine their teachings either. And one skilled in the art would have no motivation to combine the teaching of Cerretani et al. with the teachings of Sandmann et al. and/or Strulovici at least because Sandmann et al. and Strulovici do not describe formation of differentially-charged products suitable for the method described by Cerretani et al. In addition, Sandmann et al. emphasize that the substrate and products are separated by ion-exchange chromatography (which would make their assay unsuitable for the assay described by Cerretani et al.), and Strulovici emphasizes the use of non-radioactive detection.

And the cited references, even if viewed together, fail to teach, suggest, or provide motivation and enablement for Applicants' invention because, as discussed above, they fail to teach or suggest all the claim limitations.

VI. Examiner interview

The undersigned and the Examiner discussed amendments to claims 1, 2, and 13 in a telephonic interview on January 10, 2005. No agreement was reached during the interview. Applicants and the undersigned thank the Examiner for his courtesy during the interview.

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Applicants authorize the Commissioner to charge $1810.00 to Deposit Account No. **08-0750** to cover the fees for the request for continued examination and the three-month extension. Applicants believe that they do not owe any other fee(s) in connection with this submission. If, however, Applicants do owe such fee(s), the Commissioner is hereby authorized to charge those fee(s) to Deposit Account No. **08-0750**. And if there is ever any other fee deficiency or overpayment under 37 C.F.R. § 1.16 or § 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **08-0750**.

Applicants submit that the application is in condition for allowance, and request that it be allowed. Applicants request that the Examiner call the undersigned if any issues arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 CFR § 1.8

I hereby certify that this correspondence is being facsimile transmitted to facsimile number 1-703-872-9306 addressed to **Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450** on **January 24, 2005.**

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LNN/SSB/PML